Addressing the Problems of Cancer Survivors: Where Are We?

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Cancer Survivorship: Pathways to Health After Treatment
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Addressing the Problems of Cancer Survivors: Where Are We?

- Provide a framework for summarizing accomplishments and identifying challenges and opportunities in addressing problems of cancer survivors
- Illustrate this approach using a common and distressing problem experienced by cancer survivors

What Do We Know About These Problems?

- How are we defining the problem?
- How are we measuring the problem?
- How are we studying occurrence of the problem?
  - Content and timing of assessments
  - Sampling strategy

What Do We Know About These Problems?

- What have we learned about occurrence of the problem?
  - Prevalence
  - Characteristics
  - Course
  - Risk factors
  - Mechanisms

What Do We Know About These Problems?

- How are we studying management of the problem?
  - Types of interventions
  - Types of research designs
  - Samples recruited
  - Timing of the intervention

What Do We Know About These Problems?

- What have we learned about management of the problem?
  - Intervention efficacy
  - Moderators of intervention efficacy
  - Mediators of intervention efficacy
  - “Real world” effectiveness of intervention
  - Cost and cost-effectiveness of intervention

What Do We Know About These Problems?

- What do we need to accomplish to better address the problem?

Chief Concerns Following Transplantation

	In the past month
Fears of disease recurrence	77%
Energy level	57%
Difficulty remembering/concentrating	43%
Feeling tense or anxious	42%
Difficulties with medical insurance	41%
Returning to “normal”	40%
Sexual functioning	40%
Achieving life goals	39%
Poor sleep	39%
Feeling depressed	37%

Andrykowski et al., Bone Marrow Transpl 1999;24:1121-1129

MEDLINE Citations for "Neoplasms" AND "Fatigue"

- 1966-2004 919 citations
- 1966-1993 195 citations (21%)
- 1994-2004 724 citations (79%)
- 1966-2004 Breast Ca 117 citations (13%)
- 1966-2004 Age 0-18 98 citations (11%)

Defining the Problem

- Lack of consensus regarding the definition and conceptualization of fatigue in cancer patients

Measuring the Problem

- Lack of assessment tools consistent with a multidimensional conceptualization of fatigue

Examples of Multidimensional Measures

Measure	Dimensions
Brief Fatigue Inventory	severity, interference
Cancer Fatigue Scale	physical, cognitive, affective
Multidimensional Fatigue Inventory	general, physical, mental, reduced activity, reduced motivation
Piper Fatigue Scale (rev.)	behavioral/severity, sensory, affective meaning, cognitive/mood
Schwartz Cancer Fatigue Scale (rev.)	physical, perceptual

Multidimensional Approach

Fatigue Symptom Inventory

- Severity
- Duration
- Interference with quality of life

Hann et al., Qual Life Res 1998;7:301-10

Multidimensional Approach

Multidimensional Fatigue Symptom Inventory

- Physical
- Emotional
- Mental

Stein et al., Cancer Practice 1998;6:143-152; J Pain Symptom Manage 2004;27:14-23

Occurrence of the Problem

Methodological Limitations of Early Research

- Use of unidimensional measures
- Use of cross-sectional research designs
- Sampling of participants with broad range of time since tx completion
- Inclusion of different disease types in too few numbers to permit valid comparisons
- Inclusion of different treatment types in too few numbers to permit valid comparisons
- Failure to distinguish patients according to current disease status
- Absence of noncancer comparison group

Fatigue in Breast Cancer Survivors

Preliminary Studies

Aim: Determine whether women previously treated for breast cancer and with no current clinical evidence of disease were experiencing greater fatigue than women with no history of cancer

Sample 1: High dose chemotherapy
Sample 2: Standard dose chemotherapy
Sample 3: Radiotherapy

Disease and Treatment Characteristics

	GROUP		
	BMT (N=43)	ACT (N=61)	PRT (N=45)
Disease stage			
0/1	0%	25%	78%
2	30%	64%	20%
3	30%	8%	2%
4	40%	0%	0%
Mos. from dx (M, SD)	40 (25)	22 (7)	23 (20)
Mos. from tx (M, SD)	20 (16)	16 (7)	22 (14)

Fatigue Among BMT Survivors

	GROUP	
	BMT M (SD)	Comparison M (SD)
POMS-F		
Fatigue severity*	9.6 (8.1)	6.3 (6.1)
FSI		
Duration*	4.0 (2.3)	3.0 (2.3)
Interference with QoL**	2.7 (2.6)	1.5 (1.5)
MFSI		
Mental symptoms*	5.0 (5.5)	3.0 (2.7)
Emotional symptoms	4.9 (5.3)	3.7 (3.8)
Physical symptoms*	4.0 (4.2)	2.3 (2.8)

*$p \leq .05$, **$\leq .01$

Hann et al., Supportive Care Cancer 1997;5:44-52

Fatigue Among ACT Survivors

	GROUP	
	ACT M (SD)	Comparison M (SD)
POMS-F		
Fatigue severity**	8.2 (6.7)	5.3 (5.2)
FSI		
Duration	3.7 (2.5)	3.1 (2.5)
Interference with QoL*	2.0 (2.0)	1.3 (1.6)
MFSI		
Mental symptoms**	5.0 (5.1)	2.9 (3.0)
Emotional symptoms	4.5 (4.8)	3.4 (4.4)
Physical symptoms**	4.1 (4.6)	2.0 (2.6)

*$p \leq .05$, **$\leq .01$

Broeckel et al., J Clin Oncol 1998;16:1689-96

Fatigue Among PRT Survivors

	GROUP	
	PRT M (SD)	Comparison M (SD)
POMS-F		
Fatigue severity	7.4 (8.1)	6.6 (5.8)
FSI		
Duration	3.2 (2.8)	3.0 (2.2)
Interference with QoL	1.4 (2.1)	1.4 (1.5)
MFSI		
Mental symptoms	3.4 (3.6)	3.6 (3.3)
Emotional symptoms	2.9 (3.7)	3.7 (4.3)
Physical symptoms	3.6 (4.4)	3.1 (3.8)

*p≤ .05, **≤ .01

Hann et al., J Clin Psychol Med Settings 1998;5:19-33

Fatigue in Breast Cancer Survivors

- Limitations
  - Lack of randomization to treatment conditions
  - Use of cross-sectional research designs

Problems with Identifying Prevalence

- Lack of consensus for defining “clinically significant” fatigue
- Reports of prevalence are wide-ranging due, in part, to differences across studies in measures used and criteria applied
- Explore use of clinical syndrome approach as one means of standardizing definition and assessment of clinically significant fatigue

Proposed Criteria for Clinical Syndrome of Cancer-Related Fatigue

A. Six or more of the following present every day or nearly every day during same 2-week period in the past month and at least one is significant fatigue (A1).

1. Significant fatigue, diminished energy, or increased need to rest disproportionate to recent change in activity level
2. Generalized weakness, limb heaviness
3. Diminished concentration, attention
4. Decreased motivation, interest in activities
5. Insomnia, hypersomnia
6. Sleep unrefreshing, nonrestorative
7. Struggle to overcome inactivity
8. Marked emotional reactivity (sadness, frustration, irritability) to fatigue
9. Difficulty completing daily tasks attributed to fatigue
10. Short-term memory problems
11. Postexertional malaise lasting several hours

Cella et al., Oncology 1998;12:369-377

Proposed Criteria for Clinical Syndrome of Cancer-Related Fatigue (cont'd)

B. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. Evidence from history, physical examination, or laboratory findings that symptoms are a consequence of cancer or cancer therapy

D. Symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization or somatoform disorder, or delirium

Cella et al., Oncology 1998;12:369-377

Clinical Syndrome Approach

Participants (N = 51)

Age:	48 years (s.d. = 9; range = 23 - 63)
Gender:	female (75%), male (25%)
Transplant:	autologous (76%), allogeneic (24%)
Diagnoses:	breast (61%), myeloma (14%), leukemia (13%), lymphoma (10%), other (2%)
BMT stay:	23 days (s.d. = 10; range= 16 - 77)
Time elapsed:	6.9 months (s.d. = 1.1; range = 5-11)

Sadler et al., Journal of Pain & Symptom Management 2002;23:406-413

Clinical Syndrome Approach

	N	%
Two weeks of fatigue in past month (A1)	22	43%
5 or more additional symptoms (A1 + 5)	13	25%
Significant distress or impairment (B)	12	23%
Consequence of cancer or treatment (C)	12	23%
Not due to co-morbid psychiatric disorder (D)	11	21%
Criteria met for clinical syndrome	11	21%

Sadler et al., Journal of Pain & Symptom Management 2002;23:406-413

Clinical Syndrome Approach

	GROUP			
	Criteria met		Criteria not met	
	M	(SD)	M	(SD)
FSI				
Current fatigue*	4.8	(3.2)	2.6	(2.7)
Average fatigue*	4.8	(2.4)	3.1	(2.4)
Most fatigue**	7.5	(1.9)	4.5	(2.9)
Least fatigue*	3.3	(2.2)	1.7	(1.8)
No. of days fatigued***	5.8	(1.4)	3.5	(2.8)
SF-36				
Vitality**	35.0	(18.8)	57.9	(23.2)
Role-Physical*	25.0	(35.4)	54.4	(43.1)
Role-Emotional**	45.5	(37.3)	80.8	(36.1)

*$p \leq 0.05$, **≤ 0.01, ***$p<.001$

Sadler et al., Journal of Pain & Symptom Management 2002;23:406-413

Risk Factors – Demographic Variables

Variable	No. of studies	Relationship		
		None	Positive	Negative
Age	12	6	3	3
Education	9	6	0	3
Gender	5	2	3 (females)	0
Ethnicity	3	3	0	0

Risk Factors – Clinical Variables

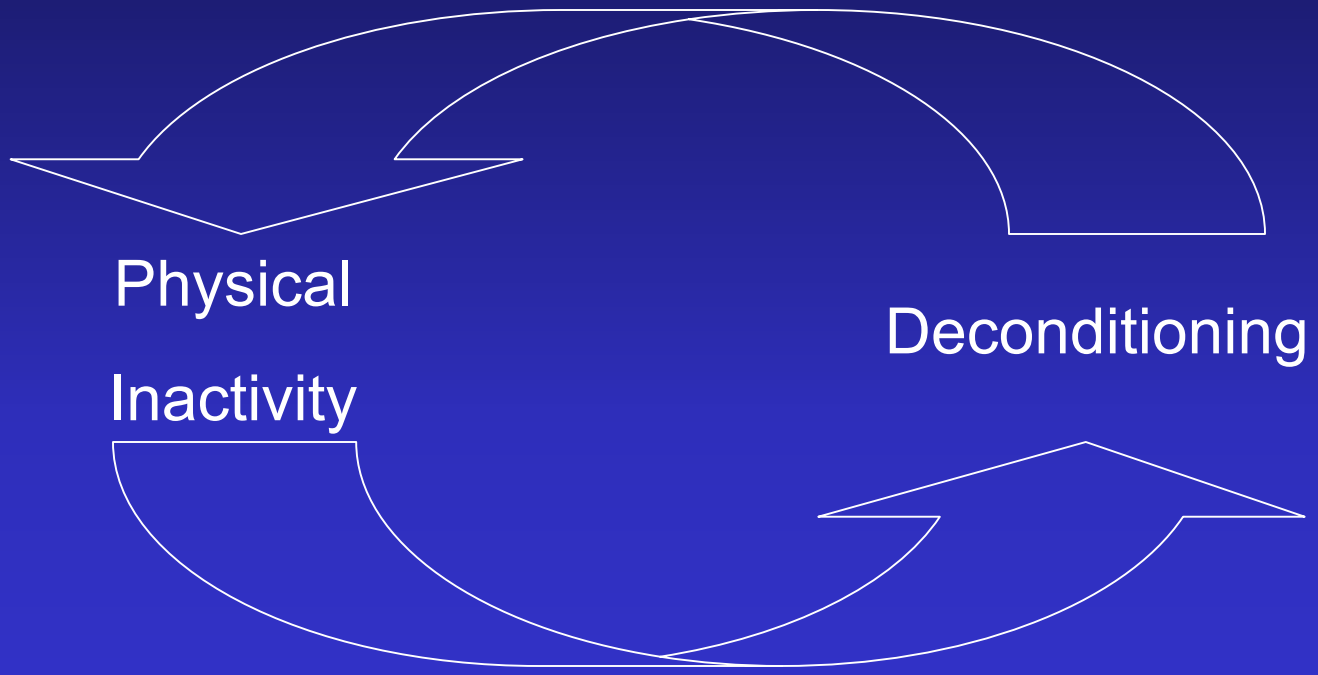
Variable	No. of studies	Relationship		
		None	Positive	Negative
Time since tx completion	14	13	1	0
Stage at dx	7	7	0	0
Cancer dx	4	3	1 (lung)	0
No. chemo cycles	3	3	0	0

Risk Factors – Clinical Variables Breast Cancer Studies

Variable	No. of studies	Relationship		
		None	Positive	Negative
Chemotherapy	5	2	3	0
Tamoxifen	5	5	0	0
Surgery type	4	4	0	0

Possible Causes of Fatigue Following Treatment Completion

- Anemia
- Physical inactivity / deconditioning



Effects of Exercise Training on QoL

Participants

Postmenopausal women (ages 50-69) with early stage breast cancer, who had completed treatment an average of 14 months previously

Design

15 week randomized clinical trial

Interventions

Exercise sessions (15 to 35 mins) on cycle ergometers 3x/wk for 15 weeks (N = 24)

No exercise (N= 28)

Courneya et al: J Clin Oncol 2003;21:1660-1668

Effects of Exercise Training on QoL

Primary Outcomes

- Cardiopulmonary function (peak oxygen consumption)
- Overall quality of life (FACT-B)

Secondary Outcomes

- Fatigue (FACT-FS)
- Additional indices of cardiopulmonary function

Courneya et al: J Clin Oncol 2003;21:1660-1668

Effects of Exercise Training on QoL

	p value
Primary Outcomes	
Peak oxygen consumption (L/min)	<.001
Overall quality of life (0-140)	<.001
Secondary Outcomes	
Fatigue (0-52)	.006
Peak power output (W)	<.001

Courneya et al: J Clin Oncol 2003;21:1660-1668

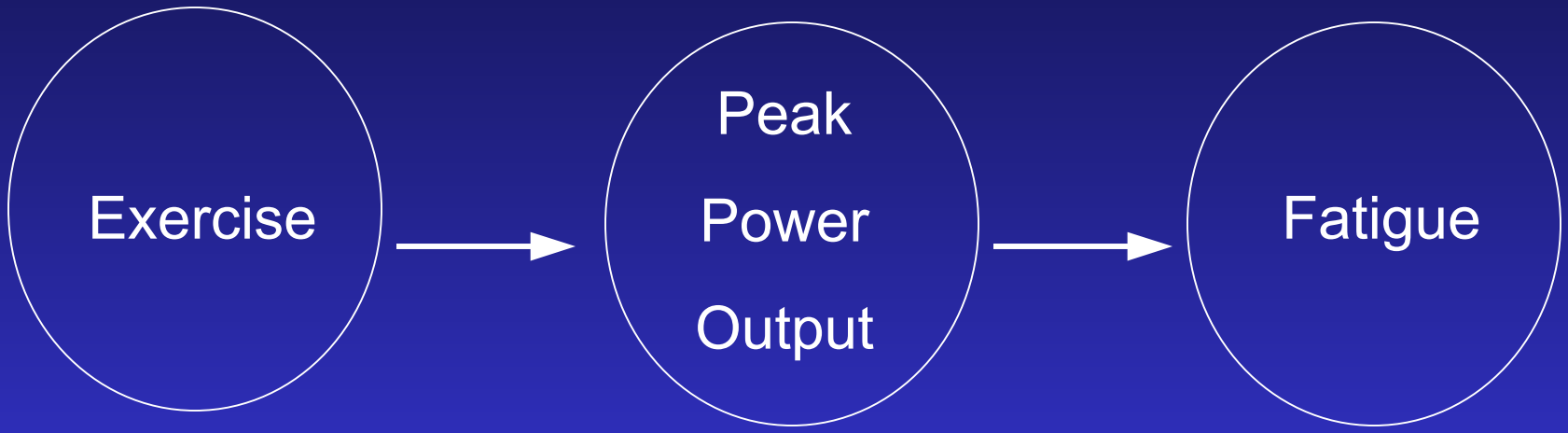
Correlations Between Changes in Cardiopulmonary Function and Fatigue

Variables	Peak Oxygen Consumption	Peak Power Output
Fatigue	-.41**	-.54**

* p < .05, **p < .01

Courneya et al: J Clin Oncol 2003;21:1660-1668

Mediational Role of Cardiopulmonary Function



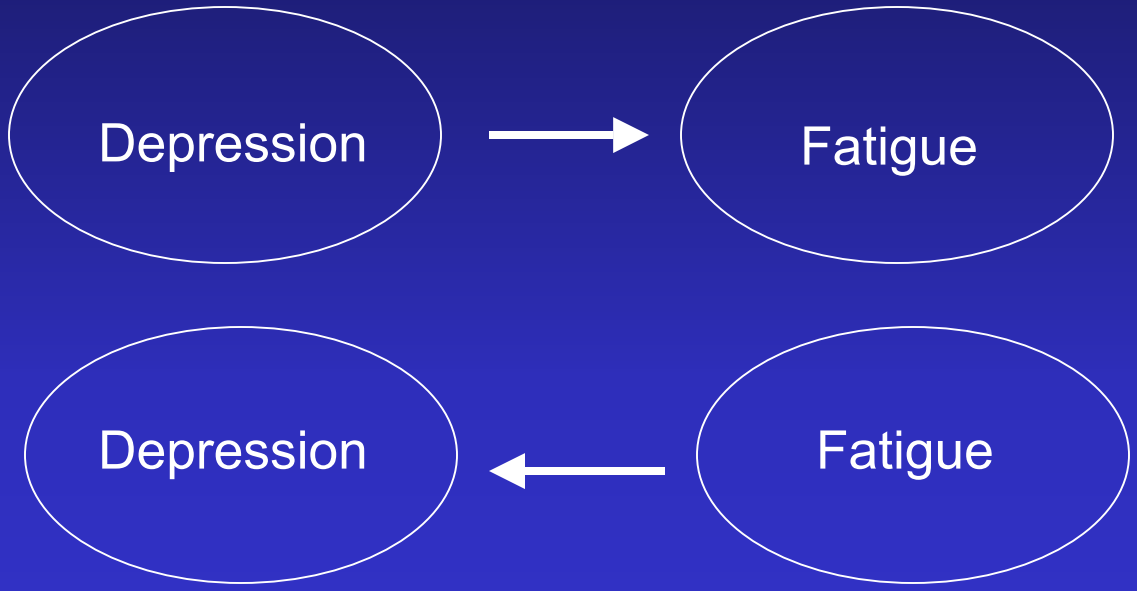
Courneya et al: J Clin Oncol 2003;21:1660-1668

Possible Causes of Fatigue Following Treatment Completion

- Anemia
- Physical inactivity / deconditioning
- Depression

Etiologic Role of Depression

- Is depression a cause or an effect of fatigue?



Stress Management Training for Chemotherapy Patients

Aim:

To compare the clinical effectiveness and economic efficiency of two methods of delivering stress management training

Jacobsen et al., J Clin Oncol 2002; 20:2851-2862

Supported by: NCI R01 CA70875; ACS PBR-99

Stress Management Training for Chemotherapy Patients

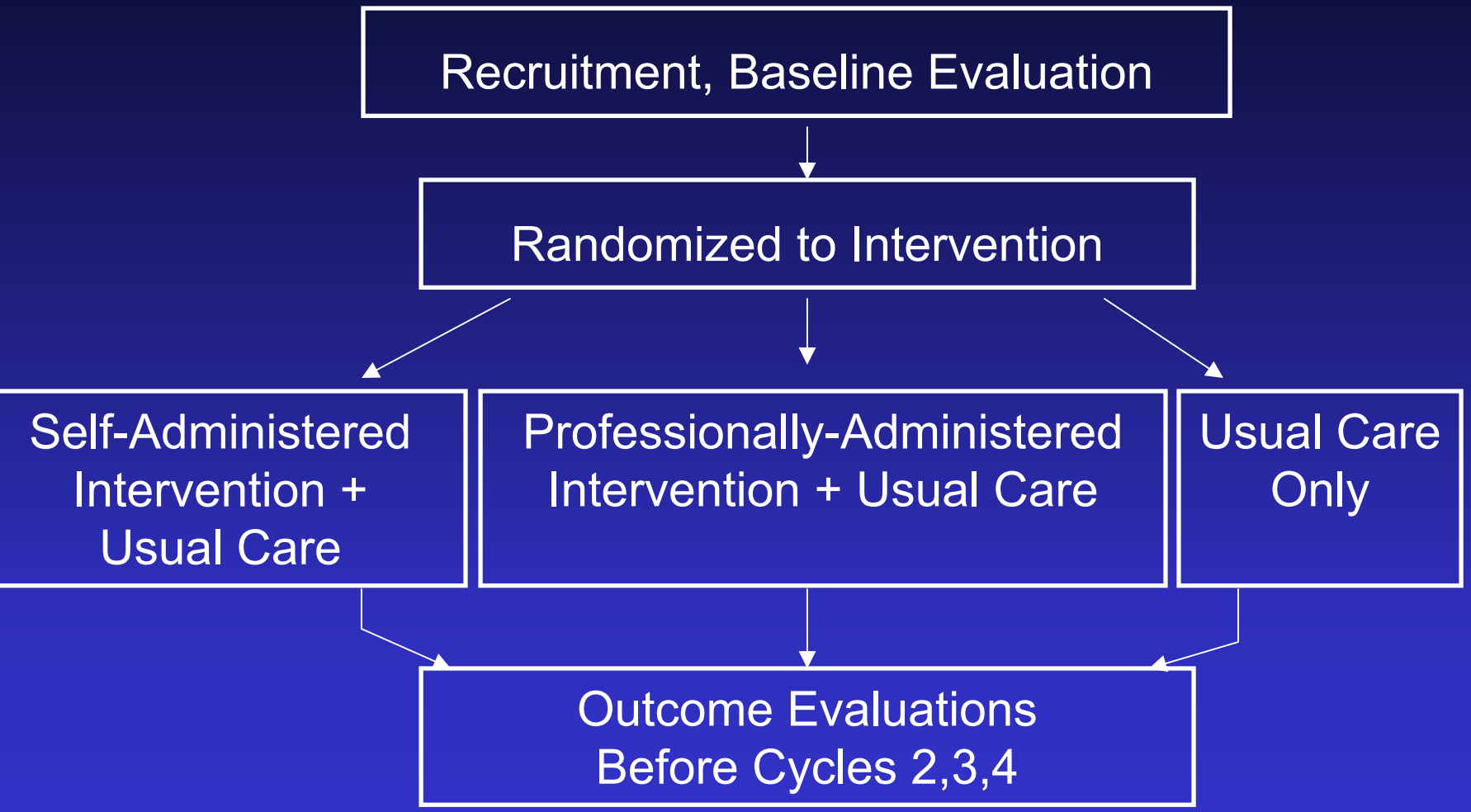
Consists of instruction in

- Deep breathing
- Progressive muscle relaxation + guided imagery
- Use of coping self-statements

Two versions

- Professionally-administered (via face-to-face meeting)
- Patient self-administered (via brochure, audiotape, and videotape)

Study Design



Stress Management for Chemotherapy Patients

Participants (N = 382)

Age: 26 to 88 years (M = 56)

Gender: female 76%

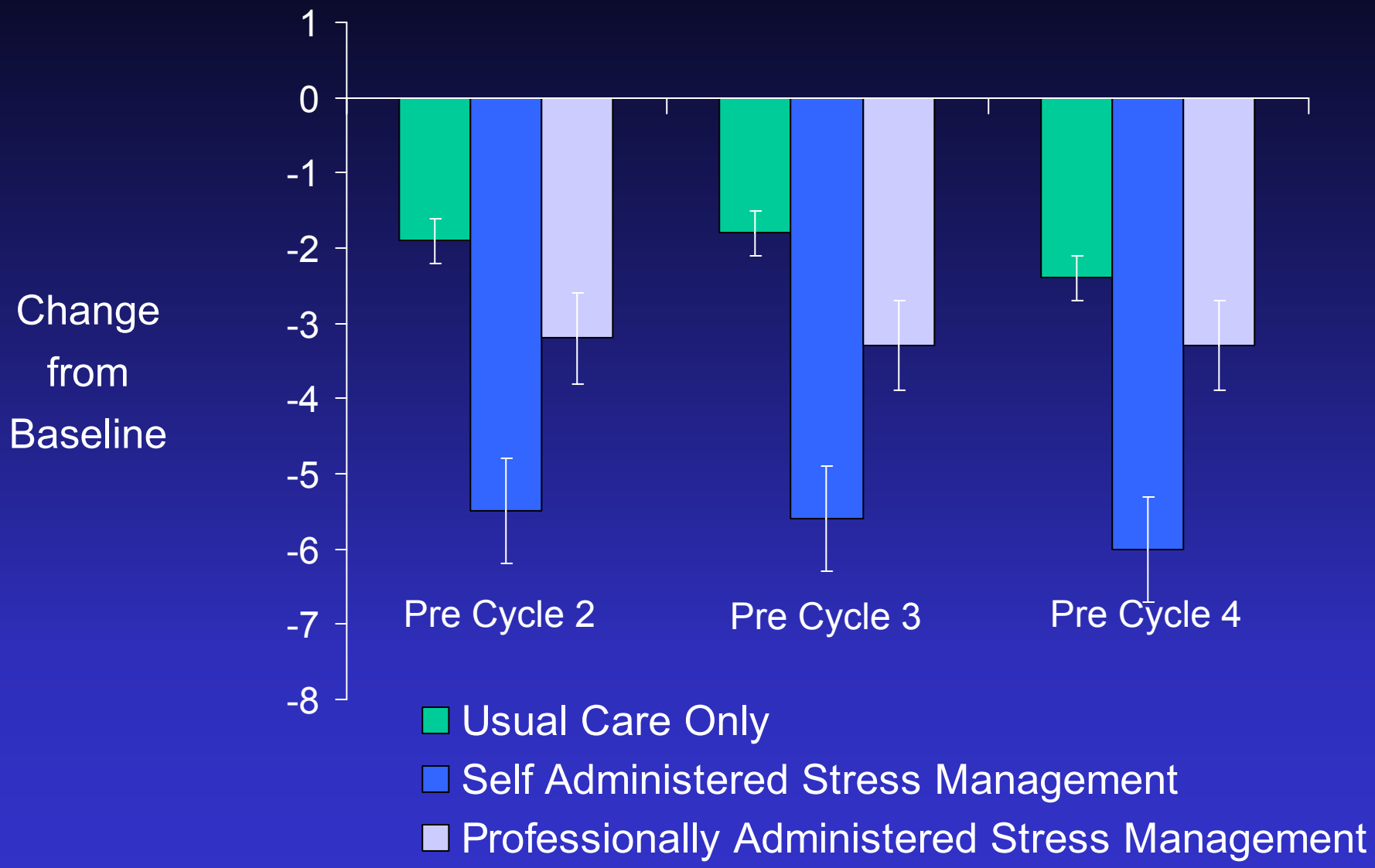
Race: white 90%

Education: attended college 63%

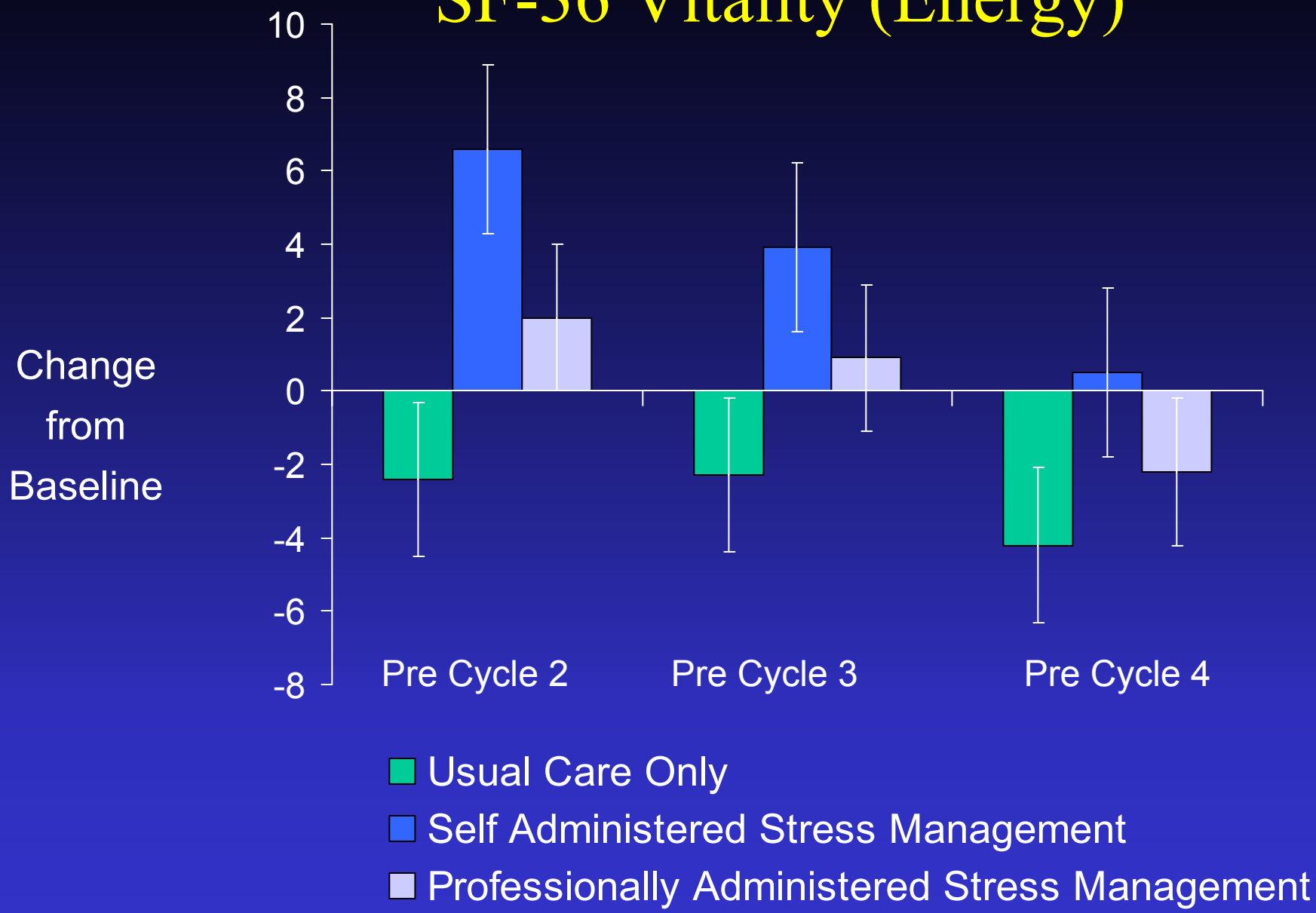
ECOG: 0 55%, 1 39%, 2 5%, 3 1%

Dx: breast 58%, lung 21%, ovarian 5%, other 14%

CES-D (Depression)



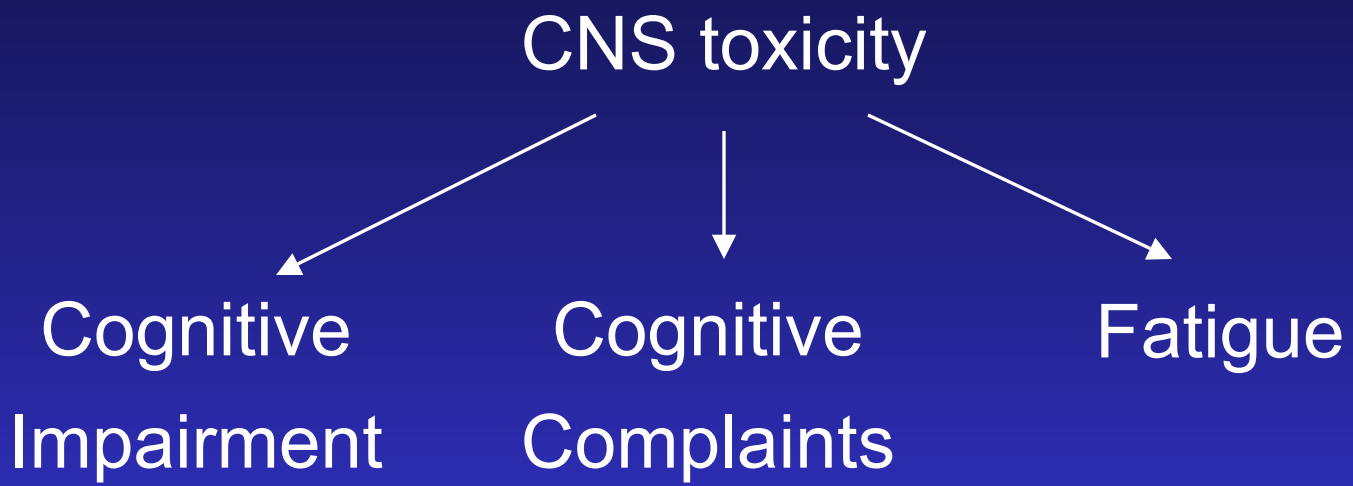
SF-36 Vitality (Energy)



Possible Causes of Fatigue Following Treatment Completion

- Anemia
- Physical inactivity / deconditioning
- Depression
- CNS toxicity

Possible Causes of Fatigue Following Treatment Completion



Possible Interpretations of Findings

- Fatigue is unrelated to CNS toxicity as evidenced by the lack of relationship with objective measures of cognitive functioning
- Lack of relationship of fatigue with objective measures of cognitive functioning may reflect use of cross-sectional research designs

Possible Causes of Fatigue Following Treatment Completion

- Anemia
- Physical inactivity / deconditioning
- Depression
- CNS toxicity
- Altered immune function

Possible Causes of Fatigue Following Treatment Completion

Cancer and/or
its treatment

↓

Increase in proinflammatory cytokines

↓

Sickness behavior
(fatigue, somnolence, decreased activity, depressed mood, cognitive disturbance)

Possible Causes of Fatigue Following Treatment Completion

- Anemia
- Physical inactivity / deconditioning
- Depression
- CNS toxicity
- Altered immune function
- Altered endocrine function

Possible Causes of Fatigue Following Treatment Completion

Treatment-induced estrogen changes

Discontinuation or contraindication of ERT

More severe menopausal symptoms

Heightened fatigue

Correlates of Fatigue Severity

	Fatigue (POMS-F)
Menopausal Symptoms (MSC)	
Total number	.55*
Vasomotor symptoms	.39*

*$p \leq .01$

Broeckel et al., J Clin Oncol 1998;16:1689-1696

Paroxetine for Hot Flashes in Women with Breast Cancer

	Pre-Tx M	(SD)	Post-Tx M	(SD)
Hot flash severity (HFQ)**	3.6	(0.5)	2.1	(1.3)
Depressive symptoms (CES-D)**	25.7	(15.0)	10.8	(10.8)
Fatigue severity (MFSI)*	35.7	(24.7)	20.2	(29.4)
Sleep quality (PSI)**	1.9	(0.7)	0.8	(0.6)

*$p \leq 0.01$, **≤ 0.001

Weitzner et al., J Pain Symptom Manage, 2002;23:337-345.

Defining and Measuring the Problem

Accomplishments

- Multidimensional conceptualizations of fatigue
- Creation and validation of self-report measures

Defining and Measuring the Problem

Challenges/Opportunities

- Lack of consensus on dimensional structure of fatigue
- Lack of consensus on optimal assessment approach
- Difficulty distinguishing fatigue from related constructs
- Lack of consensus on defining “clinically significant” fatigue

Occurrence of the Problem

Accomplishments

- Characterization of fatigue in subgroups of survivors defined in terms of both type of cancer and previous cancer treatment
- Understanding of the impact of fatigue on quality of life

Occurrence of the Problem

Challenges/Opportunities

- Limited understanding of the course of fatigue in cancer survivors
- Limited understanding of how fatigue in cancer survivors differs from fatigue in people without cancer
- Limited understanding of the prevalence of “clinically significant” fatigue in cancer survivors

Risk Factors

Accomplishments

- Demonstration that certain treatment characteristics are unlikely to be risk factors (e.g., type of surgery and tamoxifen use in early stage breast cancer survivors)

Risk Factors

Challenges/Opportunities

- Few well replicated findings regarding risk factors
- Limited understanding of the role of physical status characteristics as risk factors (e.g., co-morbidity, BMI)
- Role of genetic factors remains to be explored

Mechanisms

Accomplishments

- Accumulating evidence of the contributory role of:
  - physical inactivity and physical deconditioning
  - depression and psychological distress
  - other poorly menopausal symptoms
- Preliminary evidence of the contributory role of cytokine activity

Mechanisms

Challenges/Opportunities

- Clarification of why certain patients and not others show posttreatment elevations in cytokine activity
- Identifying treatment implications of cytokine research
- Clarification of the contributory role of CNS toxicity
- Evaluation of other possible biological mechanisms (e.g., thyroid function)

Management

Accomplishments

- Accumulating evidence of the role of exercise and physical activity interventions in relieving fatigue and the mediating role of changes in cardiopulmonary fitness
- Preliminary evidence of the role of stress management interventions in relieving fatigue

Management

Challenges/Opportunities

- Replication, extension, and dissemination of findings regarding beneficial effects of exercise and stress management
- Evaluation of promising pharmacological agents
  - Anti-depressants
  - Wake-promoting agents
  - Anti-inflammatory agents
- Design studies in which fatigue is the primary outcome

Management

Challenges/Opportunities

- Develop intervention strategies aimed at *preventing* the persistence or development of fatigue in the posttreatment period